

# Personalized Management of Post-Thrombotic Syndrome

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# Valorization



## Societal and economic relevance

Annually 1 to 2 per 1000 persons are affected by deep vein thrombosis (DVT) <sup>(1)</sup>. For the Netherlands this means that approximately 25.000 patients each year are diagnosed with DVT of whom 20% to 50% develop the chronic condition known as post-thrombotic syndrome (PTS) <sup>(2, 3)</sup>. Hence, 5000 to 12.500 patients in the Netherlands alone develop some form of post-thrombotic problems. The condition has been shown to affect the quality of life extensively and to induce significant societal costs <sup>(4-6)</sup>. Previously, the average weighted costs per person involved with PTS were estimated by our group to be €3.367 for incident PTS and €3.247 for the health state <sup>(7)</sup>. As curative therapies are absent prevention is of significant importance. Thus far however, an optimal management strategy is missing. The present thesis aimed to establish a personalized, predictive, preventive and cost-effective management approach for PTS. In order to arrive at this management strategy some important research questions needed to be answered.

First, we focused our research on the individualization of the current preventive therapy (chapter 4). This is a relevant approach for several reasons. After the initial edema is reduced, all patients with DVT are prescribed the same therapy i.e. to wear daily elastic compression stockings (ECS) for 2 years. This strategy is costly and not optimal for all patients. We hypothesized that individualized therapy would result in similar effectiveness but with the addition of better health related quality of life and positive monetary consequences (chapter 5). Second, we questioned the effect of preventive measures in the acute phase of DVT. There is no consensus as to what the best preventive therapy might be in the acute phase prior to ECS use. (Chapter 6) Based on the presumed pathophysiology of PTS, compression in the acute phase might improve venous flow and thereby possibly promote thrombus resolution and mitigate inflammatory reactions. We have investigated the effect of immediate

compression therapy after DVT diagnosis versus no compression and found that patients who received compression therapy had 15% less irreversible skin signs at 3 months, compared to those who did not receive immediate compression. Moreover, after 6 months, less obstructive vein occlusion was seen in patients who received immediate compression and that showed to be significantly related to less PTS (chapter 6). The relevance of our research question is that less PTS as a consequence of immediate compression therapy could mean less healthcare costs and better quality of life. As a third research angle we aimed to a better identification of patients at risk of PTS through development of a clinical risk score for PTS (Chapter 3). This is relevant because being able to estimate the individual patient risk of PTS development can result in patient specific and hence more effective therapy.

## **Relevance for stakeholders**

### *Patients*

Our findings will benefit the patients in several ways. In the acute phase of DVT patients now can be offered more adequate therapy that will result in better outcome (less PTS). We have shown that therapy can safely be adjusted according to the need of the individual patient. Not all patients are required to wear ECS for 2 years which will result in better quality of life and more autonomy, as not all patient are able to apply and remove the ECS independently. Moreover, wearing ECS can cause (esthetic) inconvenience and should therefore only be prescribed for prolonged duration in case the patient has a high risk of PTS development. Thus, the patients know that no unnecessarily therapy is offered.

### *Health care providers*

We developed a clear-cut stepwise management strategy for PTS that can be easily applied in practice by health care providers. As step one, we recommend prescribing immediate compression therapy in form of compression hosiery,

rather than the much expensive and inconvenient multilayer compression bandaging, to all patients with DVT in the acute phase. Step two is to estimate the individual patient risk of PTS development so that further therapy could be adjusted accordingly. To this end, we developed an easy applicable clinical risk score for PTS that uses only baseline clinical and demographic characteristics as predictors. As an internally and externally validated prediction rule, it is the first one that can be clinically applied. Step three is to individually tailor the duration of ECS based on the clinical signs and symptoms.

### *Researchers*

By showing that immediate compression therapy reduces occurrence of residual vein obstruction and consequently PTS, the results of the present thesis contributed to the confirmation of the “open vein hypothesis” that assumes that early thrombus resolution will result in less PTS because there is less vein wall damage due to the shorter duration that the thrombus is adjacent to the vessel wall. Moreover, our findings confirmed the effectiveness of ECS as such. This is an important finding because the effectiveness of compression therapy in PTS prevention had become a matter of debate. We compared a subgroup of patients without complaints and with excellent adherence to ECS therapy from the individualized strategy who were instructed to stop treatment with similar patients from the standard treatment strategy that continued treatment for 2 years. It was observed that in patients who continued ECS less PTS occurred which lead to the conclusion that compression therapy prevents PTS in general.

### *Policy makers*

Offering individualized instead of one size fits all therapy to patients suggests adequate patient oriented treatment, better health related quality of life and costs savings. We performed a cost-effectiveness analysis and found that individually tailored duration of ECS in the Netherlands would result in cost savings of 88 million euros (95% CI 31 to 144 million) measured over two years, based on 25000 cases of DVT annually. Further analysis showed that the

probability that the investigated strategy is indeed cost-effective is nearly 100%, implying that from an economic perspective too, ECS therapy should be individualized.

## **Innovativeness**

The present thesis was the first to touch upon several aspects in the management of PTS. We were the first to develop a clinically applicable risk score for PTS, to show that shortened duration of ECS is safe and feasible and to assess the effect of several forms of immediate compression therapy in the acute phase of DVT and the relation between immediate compression therapy and the occurrence residual vein occlusion and PTS, in a large study population. Additionally, as the first group we performed a cost-effectiveness analysis of individualized duration of compression therapy and contributed to the credibility of PTS pathophysiology. As such, our findings have redirected the current clinical practice in PTS prevention; patients with DVT are now prescribed immediate compression therapy in form of compression hosiery and the duration of ECS is being individualized.

## **Knowledge and products**

The current thesis resulted in six published articles in the medical journals *Phlebology*, *JTH*, *TH*, *Blood* and two articles in *the Lancet Haematology*. The first article was a narrative review explaining the theoretical background. The second article provided the first clinical risk score for PTS. The third article provided evidence for shorter duration of ECS with all the related benefits. The fourth article showed the monetary benefits of shorter duration of ECS. Article five established that all patients should have immediate compression therapy and that a compression hosiery instead of multilayer bandaging should be used. The

final article provided new insights in the relation between immediate compression therapy and residual vein obstruction. All results combined, we established a clear-cut and easily applicable personalized, predictive, preventive and cost-effective management approach for PTS.

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